One-pot Synthesis of the Indole Derivative 4-Chloro-3-sulphamoyl-*N*-(2,3-dihydro-2-methyl-1*H*-indol-1-yl)benzamide (Indapamide)

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Received July 11, 2003

New methods for the synthesis the indole derivative, Indapamide (**1**), using mixed anhydrides of the general formula R1COOCOOR2 (**2**) or DCC (N,N'-dicyclohexylcarbodiimide) (**3**), are described.

J. Heterocyclic Chem., **41**, 95 (2004).

Indapamide (**1**) (indole derivative) is the international non-proprietary name of the chemical product 4-chloro-3-sulphamoyl-*N*-(2,3-dihydro-2-methyl-1*H*-indol-1-yl)-benzamide. Indapamide (**1**) is an oral antihypertensive/diuretic, which is indicated for the treatment of hypertension, alone or in a combination with other antihypertensive drugs [1].

In the literature, several methods for the preparation of this compound have been already described. According to the processes described in the patents FR 2,003,311 [2], FR 2,663,324 [3] and FR 2,663,325 [4], 4-chloro-3-sulfamoyl-*N*-(2,3-dihydro-2-methyl-1*H*-indol-1-yl)-benzamide (**1**) is obtained in the reaction of 4-chloro-3-sulfamoylbenzoyl chloride with 1-amino-2,3-dihydro-2-methylindole or its salts in tetrahydrofuran in the presence of triethylamine. The latter compound is obtained by the reduction of the *N*-nitroso analog by the method described by Wright and Willette [2] or by the reaction of hydroxylamine-*O*-sulphonic acid with 2-methylindoline in methylene chloride in the presence of triethylamine [4].

According to the JP 54,030,159 [6] specification, Indapamide (**1**) is prepared by the reduction reaction of 4-chloro-3-sulfamoyl-*N*-(2-methyl-1-indolyl)benzamide. Patent EP 54,892 [7] reports a production method of the title compound **1** consisting in cyclisation of 1-allyl-1-phenyl-2-(3-sulfamoyl-4-chloro-benzoyl) hydrazine in the presence of Lewis or Brönsted acids.

In this note innovative routes for the preparation of Indapamide (**1**) using mixed anhydrides of the general formula R1COOCOOR2 (**2**) or using DCC (N,N'-dicyclohexylcarbodiimide) (**3**) are described.

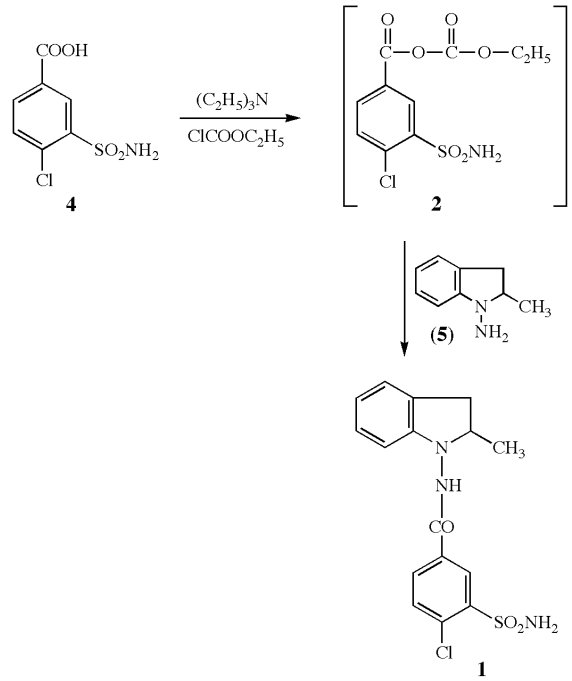
Mixed anhydrides are the most useful reagents in obtaining of amides owing to the reduced unit operations [8,9]. These reagents are usually prepared *in situ* without separation, by the reaction of carboxylic acids with tertiary amines, *e.g.*, trimethylamine, triethylamine, to the form the ammonium salt followed by further reaction of this salt with an alkyl chlorocarbonate, *e.g.*, methyl, ethylchloroformate, to form the mixed anhydride of formula **2** [10].

DCC (**3**) is commonly used as a condensation agent in peptide synthesis and in other amide bond-forming reactions of primary and secondary amines with carboxylic acids [11,12], however DCC (**3**) is rarely used in amides synthesis in large scale for the reason of difficulties with separation of the by-product, dicyclohexylurea.

In the synthesis of amide **1**, 4-chloro-3-sulfamoylbenzoic acid (**4**) and 1-amino-2-methylindoline (**5**) were used as raw materials, independently of the synthesis *i.e.* by using mixed anhydrides or DCC. The above-mentioned methods for Indapamide (**1**) synthesis are claimed in the Polish patent applications P-338964 [13] and P-340517 [14].

The sequence of Indapamide (**1**) synthesis reactions by the use 3-(amino-sulfonyl)-4-chlorobenzoyl ethyl carbonate (**2**) is shown in Scheme 1 [13].

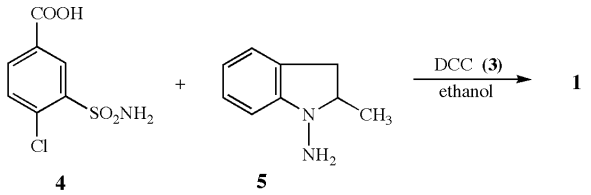
Scheme 1



In this method, Indapamide (**1**) was prepared in reaction of 1-amino-2-methylindoline (**5**) with 3-(aminosulfonyl)-4-chlorobenzoyl ethyl carbonate (**2**), obtained in the reaction of 4-chloro-3-sulfamoylbenzoic acid (**4**) with ethyl chloroformate in the presence of triethylamine. In laboratory studies, the influence of various solvents, molar relationships,

temperature and reaction time on the course of the reaction was tested. The best reaction yield, about 30%, was reached when carried out in acetone or tetrahydrofuran at temperatures below 0 °C (optimal temperature from 0 °C to –4 °C).

Scheme 2



The route of Indapamide synthesis using DCC (**3**) is shown in Scheme 2 [14]. According to this method Indapamide (**1**) was prepared by the condensation of 4-chloro-3-sulfamoylbenzoic acid (**4**) with 1-amino-2-methylindoline (**5**) in the presence of *N*,*N*'-dicyclohexylcarbodiimide (**3**) [14]. To determination the influence of solvent on the course and yield of reaction, the process was performed in various protic and aprotic solvents as well as without solvent and at temperatures below 0 °C. The results of the studies are shown in Table 1.

Table 1

Influence of Reaction Conditions on Reaction Yield of **1**

Solvent	Temp/reaction time	Yield of crude 1
Ethanol	-4 -12°C/1 – 2 h	70%
Tetrahydrofurane		65%
Methanol		42%
Acetone		15%
Dimethylformamide		10%
Methylene chloride		0%
Dioxane		0%
Without solvent		0%

The data presented in the Table demonstrate that the reaction was not observed in the presence of dioxane, methylene chloride or without solvent, because in these cases substrates were isolated from reaction mixture. The highest reaction yields (70% and 65%) were observed when ethanol or tetrahydrofurane, respectively, were applied as solvents and when the reaction was carried out at temperatures between -4 and -12 °C and optimally at temperatures between -4 °C and -8 °C.

In this method, due to the difference in solubility of Indapamide (**1**) and dicyclohexylurea in tetrahydrofurane or ethanol as a reaction solvent, we were able to obtain crude final product **1** sufficiently pure. After crystallization from a mixture of isopropyl alcohol and water the purity of Indapamide (**1**) was very high.

The structure of the Indapamide (**1**) obtained was established by using MS, ^{1}H NMR and IR methods as well as by elemental analysis. Purity of **1** was determined by HPLC analysis and by comparing the IR spectra of **1** with that of European Pharmacopoeia standard. The mass spectrum of Indapamide (**1**) shows the (see Figure 1) molecular ion with m/z 365 as well as fragment ions with m/z 218, 147 and 131.

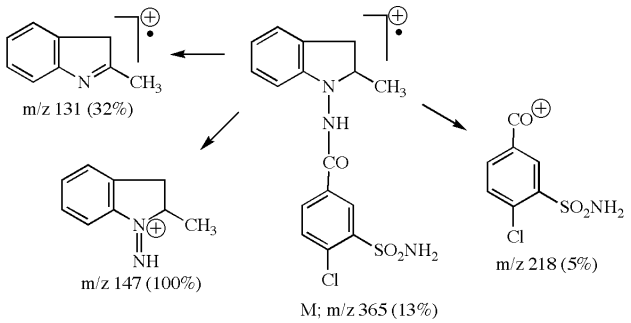
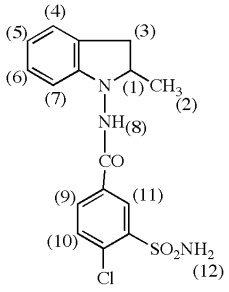


Figure 1. MS fragmentation of Indapamide (**1**).

Chemical shifts of protons (δ ppm) observed in the 2D (COSY) ^{1}H NMR spectrum of **1** are presented in Figure 2.



^{1}H NMR (DMSO); δ ppm:
1.3 (d, 3H, H-2),
2,6 and 3.15 (dd, 2H, H-3),
3.9 (wide s, 1H, H-1),
6.5 (d, 1H, H-7),
6.8 (t, 1H, H-5),
7.05 (t, 1H, H-6),
7.1 (d, 1H, H-4),
7.7 (s, 2H, H-12),
7.8 (d, 1H, H-10),
8.1 (dd, 1H, H-9),
8.5 (d, 1H, H-11),
10.5 (s, 1H, H-8)

Figure 2. ^{1}H NMR data of Indapamide (**1**).

In order to check the purity of the obtained compound **1**, IR spectrum of Indapamide (**1**) was performed and compared with the spectrum of European Pharmacopoeia standard. Correlation factor of the IR spectrum of **1** to IR spectrum of European Pharmacopoeia standard is R = 0.997777. Total impurities of **1**, detected by HPLC methods were not higher than 0.5%, which is compliant with European Pharmacopoeia requirements.

Considering both methods presented for the synthesis of Indapamide (**1**), it should be noted that the method using DCC (**3**) gives better results than that of mixed anhydrides **2**, based on yield, reaction time and the amount of solvent used. This process is efficient, economical and safe, especially using ethanol as the solvent.

EXPERIMENTAL

Elemental analyses were performed on Perkin-Elmer 2400 analyzer in the Regional Laboratory of Jagiellonian University. Mass spectra were recorded using Finnigan MAT 95 S spectrometer. ^{1}H NMR spectra were recorded in DMSO with a VARIAN (300 MHz) spectrometer and tetrametylsilane (TMS) as an internal standard. IR spectra were as KBr pellets on a Perkin-Elmer type FT-IR PARAGON 1000 spectrometer within the range of 4000 to 400 cm^{-1}. Chromatographic analyses were performed on an Alliance 2690 D liquid chromatograph with UV detector (Waters 2487 Dual λ Absorbance Detector) Waters firm.

Synthesis of 4-Chloro-3-sulfamoyl-*N*-(2,3-dihydro-2-methyl-1*H*-indol-1-yl)benzamide (**1**) Using Mixed Anhydrides of Formula **2**.

To a solution of 4-chloro-3-sulfamoylbenzoic acid (**4**) (2.35 g, 0.01mole) in acetone (25 cm^3), triethylamine (2.52 g, 0.025 mole) at a temperature between 0 °C and –4 °C ethyl chloroformate (1.41 g , 0.013 mole) and after several minutes 1-amino-2-methylindoline (**5**) (1.48 g, 0.01 mole) were added. After 1 hour of mixing, triethylamine hydrochloride was filtered off and the filtrate was evaporated under reduced pressure. To the residue, aqueous ammonium hydroxide was added to pH about 9 and the product was extracted with methylene chloride. The crude product, obtained from concentrated solution, was crystallized from a mixture isopropyl alcohol:water = 1:1.5, resulting in 1.1 mg of **1** (30% yield). A comparable reaction yield of **1** was obtained using tetrahydrofurane in place of acetone as solvent. MS and ^{1}H NMR data of **1** are presented in a main text; IR: cm^{-1} 3655 - 3068, 2966 - 2843, 1656, 1599 - 1476, 1539, 1460, 1382, 1342, 1175, 1297, 903, 847, 719.

Anal. Calcd. for $C_{16}H_{16}ClN_3O_3S$ (365.83): C, 52.53; H, 4.41; N, 11.49. Found: C, 52,74; H, 4,55; N, 11,20.

Synthesis of 4-Chloro-3-sulfamoyl-*N*-(2,3-dihydro-2-methyl-1*H*-indol-1-yl)benzamide (**1**) Using DCC (**3**).

To a solution of 4-chloro-3-sulfamoylbenzoic acid (**4**) (2.35 g, 0.01 mole) in ethanol (30 cm^3), 1-amino-2-methylindoline (**5**) (1.48 g, 0.01 mole) followed by *N*,*N*'-dicyclohexylcarbodiimide (**3**) (2.1 g, 0.01 mole) in ethanol (30 cm^3) were added at a temperature between –8 °C and –10 °C. After 2 hours of mixing the precipitated *N*,*N*'-dicyclohexylurea was filtered off and the filtrate was concentrated. To the oil residue 20 cm^3 of methylene chloride was added. After filtration and drying, crude Indapamide (**1**) was obtained with 70% yield. This product was crystallized from mixture isopropyl alcohol:water = 1:1.5. According to the described procedure, crystallized Indapamide (**1**) was obtained with 55% yield (2.0 g). All spectral data, as well as physical and chemical properties of the obtained compound **1** are the same as described above for 4-chloro-3-sulfamoyl-*N*-(2,3-dihydro-2-methyl-1*H*-indol-1-yl)benzamide (**1**) prepared by using mixed anhydrides.

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